

Crescentic transformation in primary membranous glomerulonephritis

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Summary: A 31 year old man first developed steroid-resistant idiopathic membranous glomerulonephritis in 1981. Stable normal renal function was maintained until August 1988 when he suffered a clinical relapse with heavy proteinuria and declining renal function. Immunosuppressive therapy with prednisolone and cyclophosphamide was instituted in an attempt to arrest this relapse. Despite this, he later developed acute renal failure with histological evidence of crescentic transformation of his nephritis. This unusual transformation was not associated with features of systemic vasculitis or positive anti-glomerular basement membrane and anti-neutrophil cytoplasmic antibodies.

Introduction

The prognosis of membranous glomerulonephritis (MGN) is variable; although 89% of cases maintain stable renal function over a 15 year period, 15% of those patients who present with nephrotic syndrome will develop end-stage renal failure over the same period.¹ There have been several reports of acute deterioration in renal function due to crescentic transformation,^{2–8} but a rapidly progressive course is a rare event and Beregi and Varga, in an analysis of 260 cases of membranous glomerulonephritis, did not document a single such case.⁹ The immuno-pathogenesis of this unusual transformation is unclear, but it may in some cases be associated with anti-glomerular basement membrane (anti-GBM) antibody formation.^{4,6}

A number of immunosuppressive regimens have been used in MGN in an attempt to induce clinical remission or to delay progressive renal impairment.^{10–12} These regimens were reported to be particularly helpful in those cases which showed rapid deterioration in renal function.¹¹ We report a case of crescentic transformation which arose in a patient with primary membranous glomerulonephritis during concurrent treatment with one of the suggested immunosuppressive regimens.

Case report

A previously healthy 31 year old Caucasian male presented in 1981 with a 2 month history of swollen

ankles and frothy urine. Proteinuria of 15 g/day was documented. A trial of prednisolone at a dose of 30 mg/day for 4 weeks did not lead to improvement.

On examination, he was found to be oedematous and hypertensive. The following investigations were performed: full blood counts normal, urea 7.3 mmol/l, creatinine 78 μ mol/l, creatinine clearance 116 ml/min, serum albumin 16 g/l, total protein 40 g/l and cholesterol 14.7 mmol/l. Liver function tests were normal. Hepatitis B surface antigen was negative. A full autoantibody screen was negative and serum complement and immunoglobulin levels were normal. A percutaneous renal biopsy showed Stage II membranous glomerulonephritis (Figure 1).

The steroid therapy was rapidly tapered and his oedema was satisfactorily controlled by diuretics. Between 1981 and August 1988, he remained reasonably well with a normal creatinine clearance, although proteinuria persisted in the range of 7 to 13 g/day. Serum albumin fluctuated between 23 and 35 g/l. The maintenance treatment was: atenolol 100 mg/day, frusemide varying between 80 and 250 mg/day and spironolactone varying between 25 and 150 mg/day.

In October 1988 he developed a clinical relapse. He gained weight and his proteinuria increased to 17 g/day. His serum creatinine rose to 180 μ mol/l, creatinine clearance fell to 59 ml/min and serum albumin to 25 g/l. In view of this deterioration, he was started on prednisolone 60 mg/day tapering by 10 ml/day each week and cyclophosphamide 2 mg/kg/day (150 mg/day), a regimen suggested by West.¹⁰

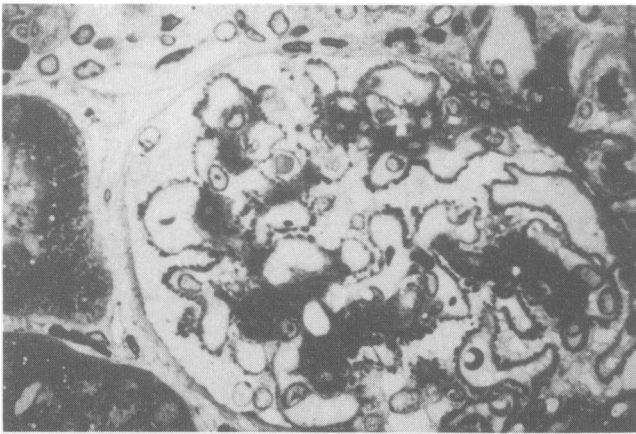


Figure 1 Methanamine silver stain $\times 40$. Diffuse capillary wall thickening with formation of spikes of basement membrane.

By the end of December 1988, having been on immunosuppressive treatment for 4 weeks, he presented with a 2 week history of intense nausea, intermittent diarrhoea and vomiting, culminating with 3 days of anuria. Urea was raised at 70 mmol/l and creatinine 2245 $\mu\text{mol/l}$. Ultrasound demonstrated kidneys of normal sizes and morphology and no evidence of renal vein thrombosis. A DTPA nuclear scan showed poor renal perfusion bilaterally. He was treated with intravenous fluids and haemodialysis. Additional investigations carried out on admission were as follows: haemoglobin 7.2 g/dl, serum albumin 27 g/l and total protein 48 g/l. Autoantibody screen was again negative and serum complement and immunoglobulin levels were within the normal range. Anti-GBM and anti-neutrophil cytoplasmic antibodies (ANCA) were undetectable in the serum on two separate occasions.

A second percutaneous renal biopsy was performed and showed acute crescentic transformation on a background of primary membranous glomerulonephritis (Figure 2). Immunoperoxidase stain failed to reveal any linear IgG staining of the GBM but a heavy granular capillary wall IgG staining was seen. No obvious cause for this transformation was identified. He remained dialysis-dependent. The cyclophosphamide was later stopped due to prolonged leucopenia, and in view of the severity of the histological findings and persistent oliguria, the prednisolone was also tapered. After 15 months of maintenance haemodialysis, he was successfully transplanted in April 1990.

Discussion

Acute crescentic transformation is a rare event in patients with membranous glomerulonephritis. In

the case reported here, after 7 years of stable renal function the patient experienced a clinical relapse with deterioration in renal function which pursued a rapidly progressive course with crescentic transformation during concomitant treatment with prednisolone and cyclophosphamide.

Several authors have reported acute crescentic transformation in patients with primary membranous glomerulonephritis²⁻⁸ and it appears that in some cases this is associated with the appearance of anti-GBM antibodies. In these reports, a total of 9 cases were documented, of which three were associated with detectable anti-GBM antibodies in the serum by indirect immunofluorescence.^{4,6} An additional case, by implication, would have had positive anti-GBM antibodies present, as IgG eluted from the affected kidney was shown to bind to the GBM of both human and monkey kidneys.² In 5 cases the anti-GBM antibodies were either not measured^{3,4} or were negative.^{5,7,8} It was suggested that the release of GBM antigens during the glomerular injury sustained as a result of the membranous process may contribute to the pathogenesis of anti-GBM antibody production and thus trigger further acute immunological insults to the glomeruli with the subsequent formation of crescents.²

The possibility of underlying anti-GBM disease in this case is unlikely because anti-GBM antibodies were not detected in the serum. Although their absence cannot be certain, as we were unable to perform the elution studies as described by Klassen *et al.*,² this view is further supported by the lack of linear IgG deposition in the glomeruli of the present case. We are not aware of any studies which examined the ANCA status of this small subgroup of patients with primary MGN, but in the case described here there was no histological evidence of vasculitis and ANCA was not detected.

The clinical course of the present case and that of

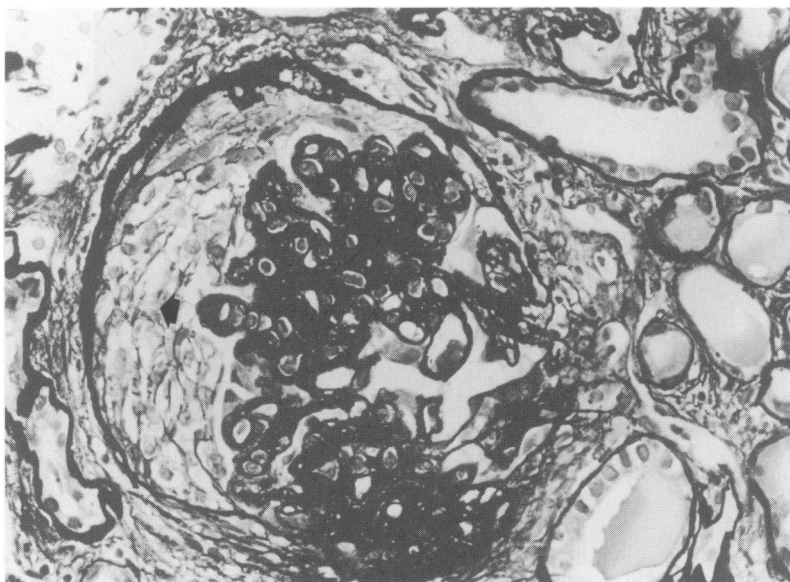


Figure 2 Methenamine silver stain $\times 16$. Gross capillary wall thickening with formation of a cellular crescent within Bowman's capsule (arrowed).

the others reported in the literature suggest that immunosuppression is not useful in patients with primary MGN once crescentic transformation has supervened. Because anti-GBM disease is prone to recur in the grafts of patients transplanted while the

disease is still active,¹³ these patients should be screened carefully for evidence of anti-GBM disease in order to determine the optimal time for transplantation.

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